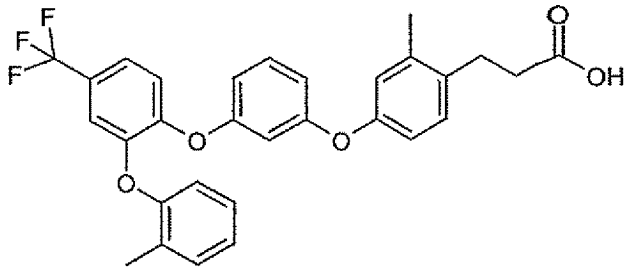
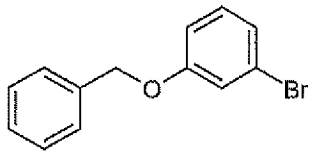
Example 89

3-{2-Methyl-4-[3-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



Step A

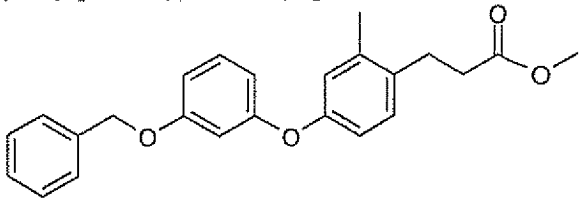
3-Benzyloxy-1-bromobenzene



A mixture of 3-bromophenol (10.0 g, 57.8 mmol) and 325 mesh potassium carbonate (8.79 g, 63.6 mmol) in DMF (100 mL) is treated dropwise with benzyl bromide (9.89 g, 57.8 mmol) and then stirred for 20 hours at room temperature under N_2. The reaction is filtered, and the filtrate is acidified with 1 N HCl. The mixture is then diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 10/1 hexanes/ethyl acetate to afford about 14.55 g (96%) of the titled compound. $R_f = 0.86$ (4/1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$).

Step B

3-[4-(3-Benzyloxy-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

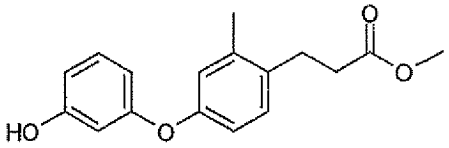


A mixture of 3-benzyloxy-1-bromobenzene (14.53 g, 55.2 mmol), 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (10.72 g, 55.2 mmol) cesium carbonate (21.59 g, 66.3 mmol), and 2,2,6,6-tetramethyl-3,5-heptanedione (2.54 g, 13.8 mmol) in 1-methyl-2-pyrrolidinone (100 mL) is purged with N_2, and then copper (I)

chloride (2.73 g, 27.6 mmol) is added. The reaction mixture is heated to 120 °C for 18 hours under N_2. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using a gradient of 19/1 to 9/1 hexanes/ethyl acetate to afford about 10.54 g (51%) of the titled compound. $R_f = 0.53$ (100% hexanes). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{24}H_{24}O_4$ 376, found 377 (M + 1, 100%).

Step C

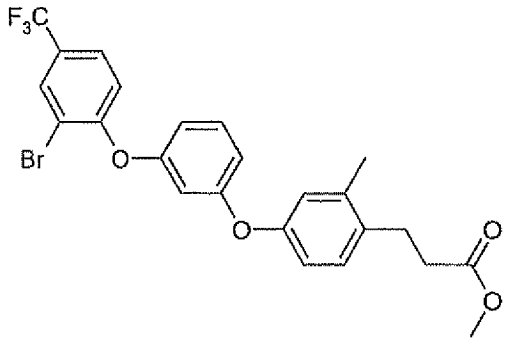
3-[4-(3-Hydroxy-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



A mixture of 3-[4-(3-benzyloxy-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (10.54 g, 28.0 mmol) and 10% Pd/C (5 g) in ethyl acetate (150 mL) is purged with N_2, and then purged with H_2, which is stirred under a hydrogen balloon. Upon reaction completion, the mixture is filtered through Hyflo, and the solvent is removed *in vacuo* to afford about 8.18 g (100%) of the titled compound. $R_f = 0.59$ (4/1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{17}H_{18}O_4$ 286, found 287 (M + 1, 100%).

Step D

3-{4-[3-(2-Bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester:



A mixture of 3-[4-(3-hydroxy-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (8.18 g, 28.6 mmol), 3-bromo-4-fluorobenzotrifluoride (6.80 g, 28.0 mmol)

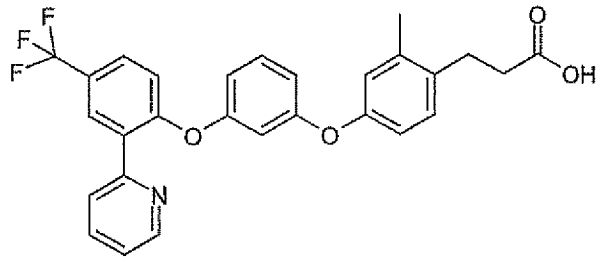
and 325 mesh potassium carbonate (4.64 g, 33.68 mmol) in dry DMSO (80 mL) is heated to 100 °C and stirred for about 6 hours under N_2. The reaction is cooled and acidified with 1 N HCl. The mixture is then diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 15/1 hexanes/ethyl acetate to afford about 11.74 g (81%) of the titled compound. $R_f = 0.76$ (9/1 hexanes/EtOAc). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{24}H_{20}O_4F_3Br$ 509, found 526 and 528 ($M + NH_4$, 100%).

Step E

The title compound is prepared according to Example 38 by using o-cresol and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 229 mg (21%). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{25}O_5F_3$ 522, found 523 ($M + 1$, 100%).

Example 90

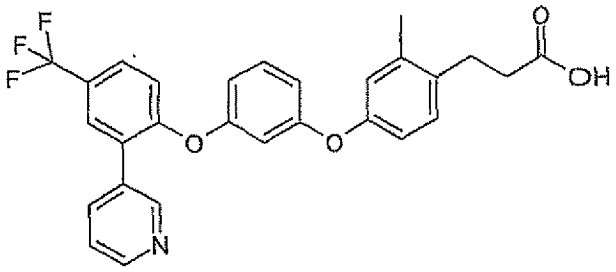
3-{2-Methyl-4-[3-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 2-tributylstannyl pyridine and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 29 mg (14%). ^1H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{28}H_{22}NO_4F_3$ 493, found 494 ($M + 1$, 100%).

Example 91

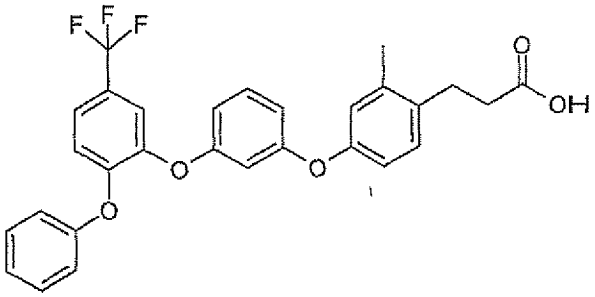
3-{2-Methyl-4-[3-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 3-pyridyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 277 mg (88%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{28}H_{22}NO_4F_3$ 493, found 494 (M + 1, 100%).

Example 92

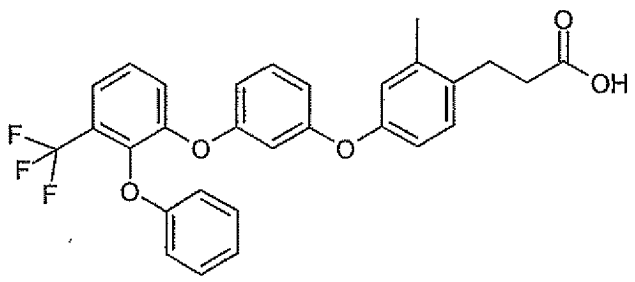
3-{2-Methyl-4-[3-(2-phenoxy-5-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 85 by using 2-phenoxy-5-trifluoromethyl-phenol and 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford about 35 mg (11%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{23}O_5F_3$ 508, found 509 (M + 1, 100%).

Example 93

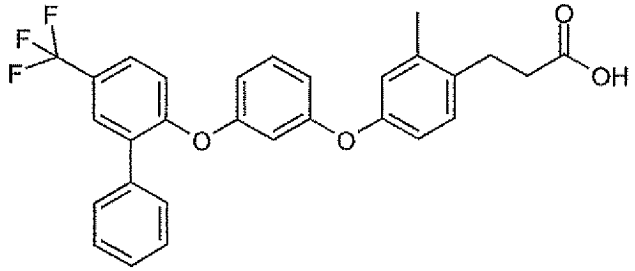
3-{2-Methyl-4-[3-(2-phenoxy-3-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 85 by using 2-phenoxy-3-trifluoromethyl-phenol and 3-[4-(3-bromo-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester to afford about 11 mg (6%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{23}O_5F_3$ 508, found 509 (M + 1, 100%).

Example 94

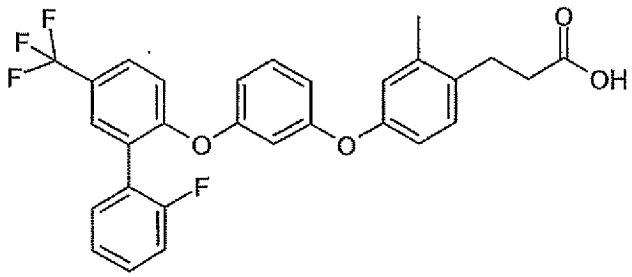
3-{2-Methyl-4-[3-(5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using phenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 74 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{23}O_4F_3$ 492, found 493 (M + 1, 100%).

Example 95

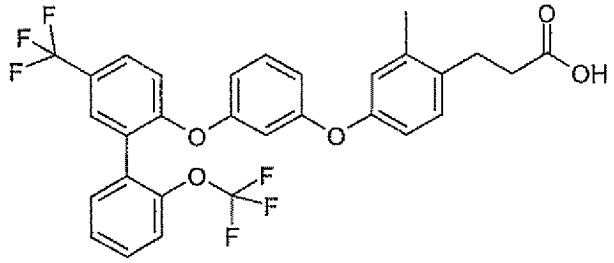
3-{4-[3-(2'-Fluoro-5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 2-fluorophenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 132 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{22}O_4F_4$ 510, found 511 (M + 1, 100%).

Example 96

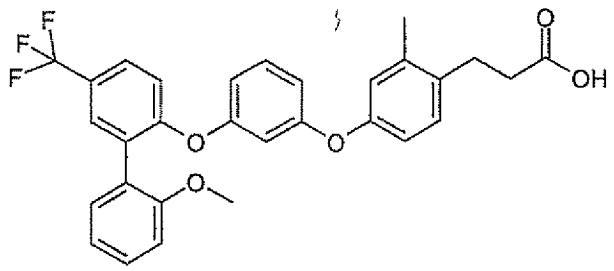
3-{2-Methyl-4-[3-(2'-trifluoromethoxy-5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 2-trifluoromethoxyphenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 94 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{22}O_5F_6$ 576, found 577 (M + 1, 100%).

Example 97

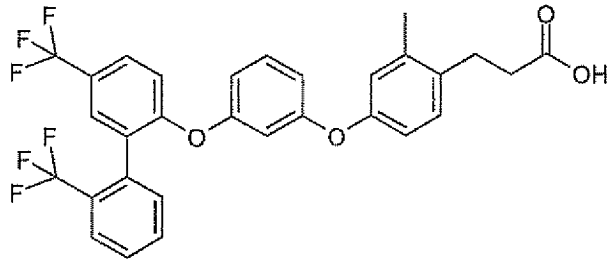
3-{4-[3-(2'-Methoxy-5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 2-methoxyphenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 102 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{25}O_5F_3$ 522, found 523 (M + 1, 100%).

Example 98

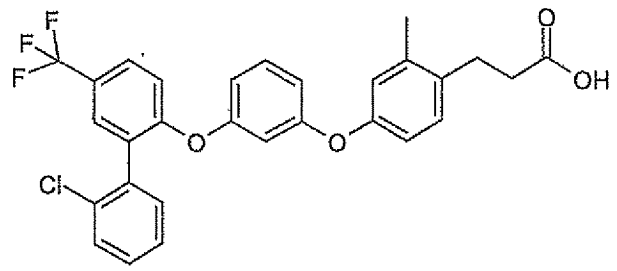
3-{4-[3-(5,2'-Bis-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 2-trifluoromethylphenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 108 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{22}O_4F_6$ 560, found 561 (M + 1, 100%).

Example 99

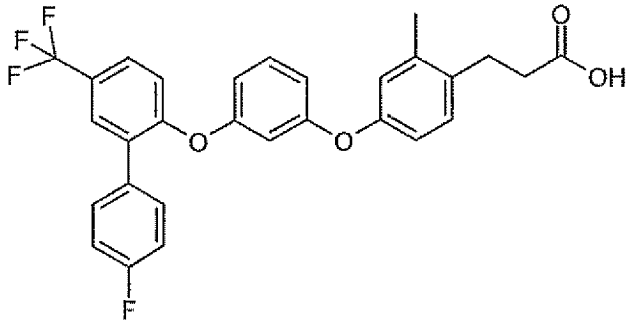
3-{4-[3-(2'-Chloro-5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 2-chlorophenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 122 mg (66%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{22}O_4F_3Cl$ 526, found 527 and 529 (M + 1 and M + 3, 100%).

Example 100

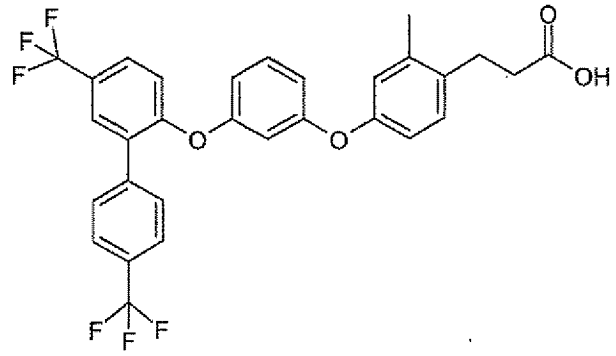
3-{4-[3-(4'-Fluoro-5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 4-fluorophenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 129 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{22}O_4F_4$ 510, found 511 (M + 1, 100%).

Example 101

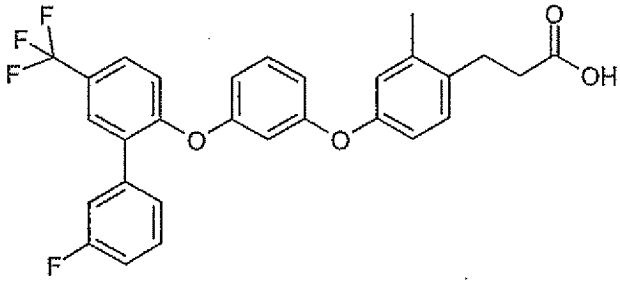
3-{4-[3-(5,4'-Bis-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 4-trifluoromethylphenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 99 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{22}O_4F_6$ 560, found 561 (M + 1, 100%).

Example 102

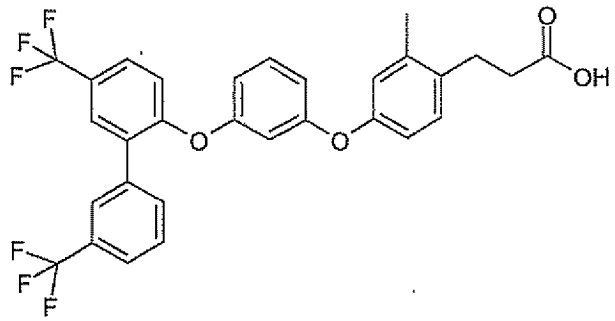
3-{4-[3-(3'-Fluoro-5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 4-trifluoromethylphenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 115 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{22}O_4F_4$ 510, found 511 (M + 1, 100%).

Example 103

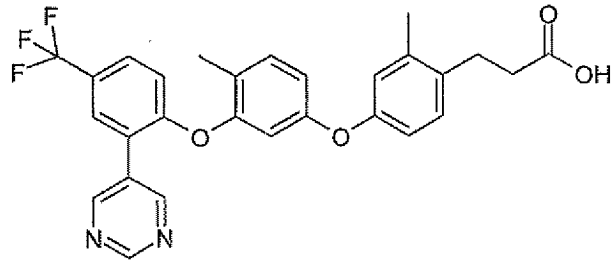
3-{4-[3-(5,3'-Bis-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using 3-trifluoromethylphenyl boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 112 mg (63%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{30}H_{22}O_4F_6$ 560, found 561 (M + 1, 100%).

Example 104

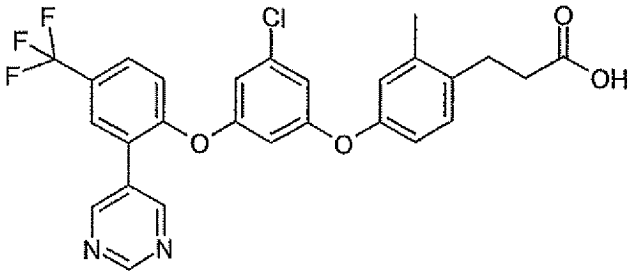
3-{2-Methyl-4-[4-methyl-3-(2-pyrimidin-5-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using pyrimidine-5-boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-chloro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester to afford about 66 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{28}H_{23}O_4F_3N_2$ 508, found 509 (M + 1, 100%).

Example 105

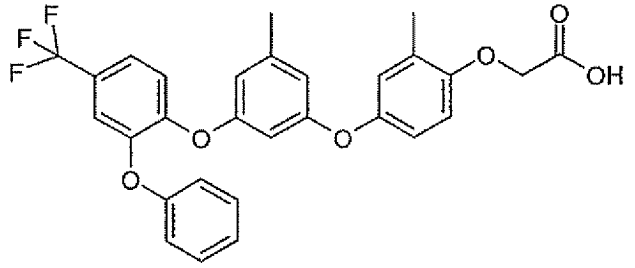
3-{4-[3-Chloro-5-(2-pyrimidin-5-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid



The title compound is prepared according to Example 89 by using pyrimidine-5-boronic acid and 3-{4-[3-(2-bromo-4-trifluoromethyl-phenoxy)-5-chloro-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester to afford about 31 mg (22%). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{27}H_{20}O_4F_3N_2Cl$ 528, found 529 (M + 1, 100%).

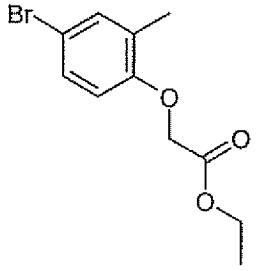
Example 106

{2-Methyl-4-[3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenoxy}-acetic acid



Step A

(4-Bromo-2-methyl-phenoxy)-acetic acid ethyl ester

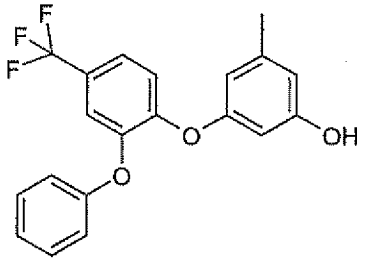


A mixture of 4-bromo-2-methylphenol (10.0 g, 53.5 mmol) and 325 mesh potassium carbonate (11.08 g, 80.2 mmol) in DMF (100 mL) is treated dropwise with bromoethyl acetate (10.71 g, 64.1 mmol) and then stirred for about 20 hours at room

temperature under N_2. The reaction is filtered, and the filtrate is acidified with 1 N HCl. The mixture is then diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 5/1 hexanes/ethyl acetate to afford about 15.01 g (100%) of the titled compound. R_f = 0.33 (4/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$).

Step B

3-Methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenol



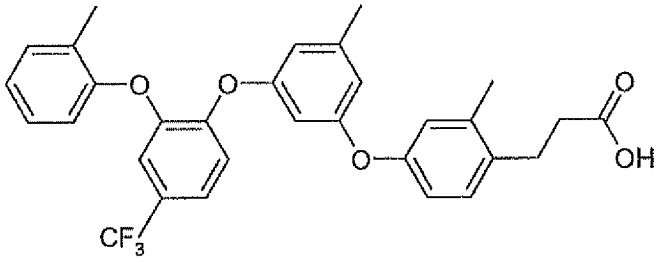
Example 63, step A intermediate (7.0 g, 16.0 mmol), phenol (3.0 g, 32.0 mol), cesium carbonate (10.43 g, 32.0 mol), and 2,2,6,6-tetramethyl-3,5-heptanedione (0.74 g, 4.01 mmol) in 1-methyl-2-pyrrolidinone (70 mL) is purged with N_2, and then copper (I) chloride (0.79 g, 7.98 mmol) is added. The reaction mixture is heated to 120 °C for 20 hours under N_2. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 14/1 hexanes/ethyl acetate to afford 5.30 g (74%) product. R_f = 0.48 (4/1 hexanes/ethyl acetate)

A mixture of 5.30 g of obtained above and 10% Pd/C (2.50 g) in ethyl acetate (150 mL) is purged with N_2 and then H_2, and the mixture is stirred under a H_2 balloon at rt. Upon completion of the reaction, the mixture is filtered through hyflo, and the solvent is removed *in vacuo* to afford crude product that is purified by flash chromatography using 5/1 hexanes/ethyl acetate to afford 3.83 g (90%) of the title compound. R_f = 0.28 (4/1 hexanes/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calculated for $C_{20}H_{15}F_3O_3$ 360, found 359 (M - 1, 100%).

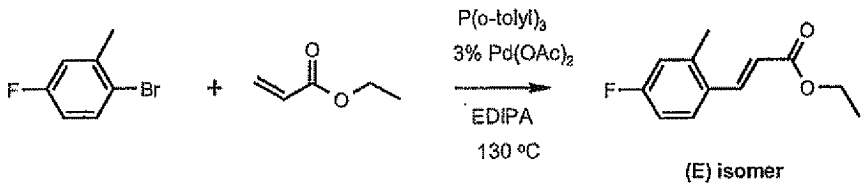
Step C

Intermediates 3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenol (0.49 g, 1.36 mmol) and (4-bromo-2-methyl-phenoxy)-acetic acid ethyl ester (0.37 g, 1.36 mol) were combined with cesium carbonate (0.53 g, 1.63 mol), and 2,2,6,6-tetramethyl-3,5-heptanedione (0.063 g, 0.342 mmol) in 1-methyl-2-pyrrolidinone (10 mL) is purged with N_2, and then copper (I) chloride (0.067 g, 0.677 mmol) is added. The reaction mixture is heated to 120 °C for 20 hours under N_2. The mixture is diluted with water and extracted with Et_2O. The organic layer is dried (Na_2SO_4), and the solvent is removed *in vacuo* to afford crude product that is absorbed on silica gel and purified by flash chromatography using 9/1 hexanes/ethyl acetate to afford 0.094 g (13%) {2-methyl-4-[3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenoxy}-acetic acid ethyl ester that was saponified with ethanol and 5 N NaOH to afford 0.072 g (81%) ^{1}H NMR (400 MHz, $CDCl_3$); MS (ES^+) *m/z* mass calcd for $C_{29}H_{23}O_6F_3$ 524, found 525 (M + 1, 100%).

Example 107



Step A

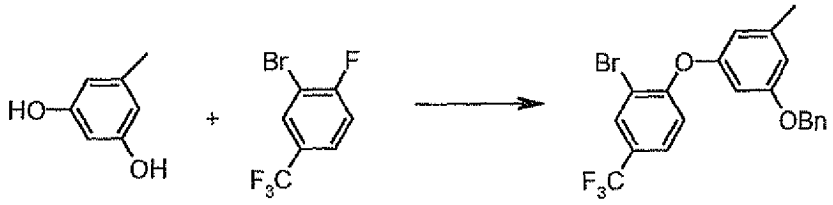


(E) isomer

A 12-L flask is equipped with a heating mantle, air stirrer, condenser, addition funnel and N_2 inlet/outlet using a Firestone valve. The flask is thoroughly purged with nitrogen, and then charged 2-bromo-5-fluorotoluene (500.0 g, 2.65 moles), DMF (1100 mL), ethyl acrylate (278.3 g, 2.78 moles), and *N,N*-diisopropylethylamine (EDIPA) (359.3 g, 2.78 moles) to form a solution. Tri-*o*-tolylphosphine (48.7 g, 0.16

moles) and palladium(II) acetate (17.8 g, 0.08 moles) are added to form a brown-orange suspension. After heating the suspension to about 115-120^{0}C, the reaction is monitored by GC. After approximately 4 hours, about <1% starting material is remained, and the reaction is deemed complete. After cooling the reaction to rt, a saturated aq. NH_4Cl solution (1.5 L) and EtOAc (3.0 L) are added to form a biphasic solution. The solution is transferred to a separatory funnel, and the layers are separated. After extracting the aqueous layer with EtOAc (3.0 L), the combined organic layers are washed with 10% aq. NH_4Cl solution (2 x 1.0 L). The organic layer is dried over Na_2SO_4 and filtered. The filtrate is concentrated to an oil to yield crude product (672 g). Purification by Kugelrohr distillation (bp=110-120^{0}C @ 1.0mm Hg) yielded compound A (507.8 g, 92.2%) as a clear light yellow oil. ^{1}H-NMR($CDCl_3$, 300MHz) δ 7.89 (d, 1H), 7.56 -7.48 (m, 1H), 6.94-6.84 (m, 2H), 6.29 (d, 1H), 4.26 (q, 2H), 2.42 (s, 3H), 1.331 (t, 3H).

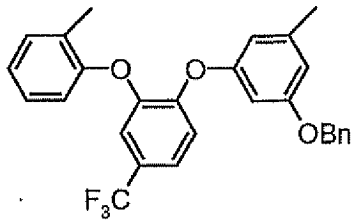
Step B



To a solution of orcinol (25.54 g, 0.20 mol) in DMSO (250 mL) is added 5 N NaOH solution (64 mL). The mixture is stirred at 90 °C for 15 min., and then 3-bromo-4-fluoro-benzotrifluoride (25.0 g, 0.10 mol) is added dropwise over 10 minutes. The mixture is stirred at 90°C for 1.5 h, cooled to rt, diluted with water (300 mL), and extracted with hexanes (3 × 200 mL). The aqueous layer is split into 2 portions with equal volume. One portion is extracted with EtOAc (3 × 200 mL). The combined EtOAc layers are washed with 5 N HCl (150 mL) and brine (150 mL), and then dried over Na_2SO_4 and concentrated to provide 15.3 g (67%) of the desired product.

Under nitrogen purge, the compound obtained from the above procedure, CH_3CN (8.6 vol.), 325 mesh K_2CO_3 (3 equiv.) are combined and stirred, and then benzyl bromide (1.02 equiv.) in CH_3CN (1.4 vol.) is added slowly to the solution. Reaction is warmed to reflux (82°C) and traced via TLC. Upon the reaction is completed, reaction contents are cooled and filtered. Filter cake is washed with 5 volumes of CH_3CN, and filtrate is concentrated to provide an oil.

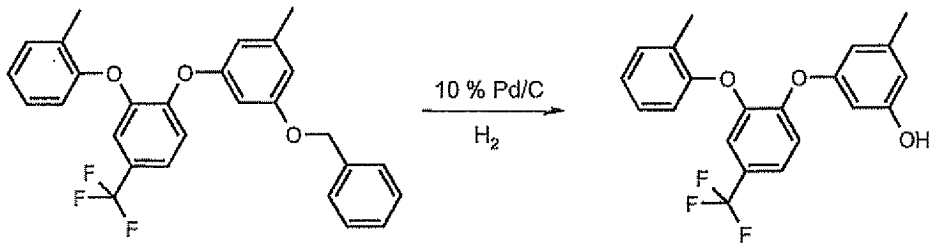
Step C



In a 12 L flask with N_2 atmosphere is added the compound obtained from Step C (464 g, 1.06 mol), *o*-cresol (229.6 g, 2.12 mol), Cs_2CO_3 (690.7 g, 2.12 mol), and 3 L ethyleneglycol diethyl ether. The mixture is stirred at rt for 1 h with N_2 bubbling subsurface. CuCl (26.24 g, 0.265 mol) is added followed by tetramethyl heptanedione (THMD) (19.53 g, 0.106 mol). The mixture is heated at 120 °C for 18 h. Reaction progress is monitored by GC. About 3.5 L MTBE is added, and the solid is filtered and rinsed with 1 L MTBE. The filtrate is diluted with 5 L H_2O, stirred 10 min and the organic layer is separated. The aqueous layer is washed with 2.5 L MTBE. The combined organic layers are washed with 2 × 2 L conc. NH_4OH, 2 L 2.5 N NaOH, sat. NH_4Cl, and then dried over Na_2SO_4 for 20 min, filtered and evaporated on 55 °C bath. About 517 g (104.8% crude yield) of dark brown oil is collected.

About 3.5 kg of silica is dry packed on glass funnel, and then treated with 15% CH_2Cl_2/heptane. The oil is dissolved in 250 mL CH_2Cl_2. About 1 L heptane is added, loaded on column, and then eluted as follows: 15% CH_2Cl_2/heptane, cuts 1-9, 2 L; 10-12 3.5 L; 20% CH_2Cl_2/heptane cuts 13-15, 3.5 L. Cuts 4-11 are collected and concentrated to provide about 447.1 g product which is used in the next step.

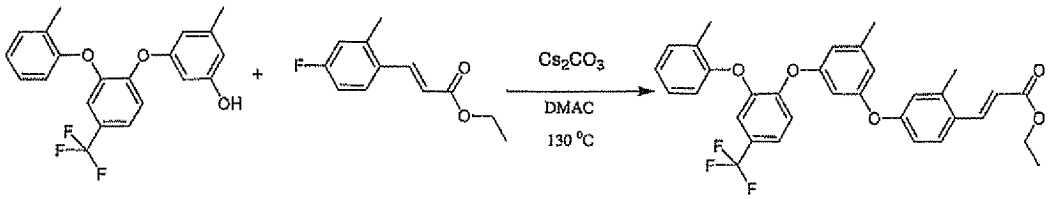
Step D



A slurry of 10% Pd/C (54.5 g) and abs. EtOH (0.4 L) are charged to the autoclave reactor (T86A) followed by a solution of the compound obtained from Step C (303.1 g) in abs. EtOH (2.0 L). The solution is stirred under H_2 (40 psi) for 2 hours. The

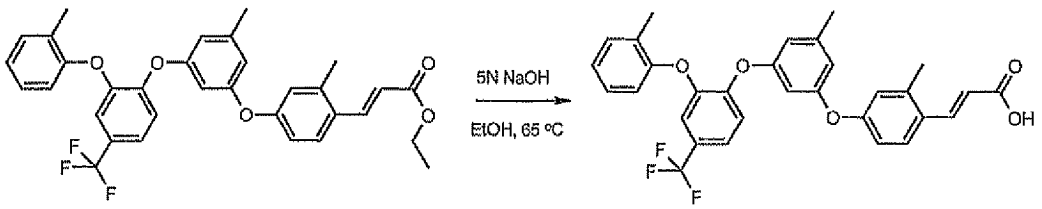
reaction is filtered and washed with abs. EtOH (1.2 L). The filtrate is concentrated to an oil, and then purified by Kugelrohr distillation. Low boiling impurities are removed (bp = 175-180°C @ 1.0mm Hg) to afford the product as a thick amber oil. ^{1}H-NMR($CDCl_3$, 300MHz) δ 7.38-7.00 (m, 6H), 6.82 (d, 1H), 6.38 (d, 2H), 6.25 (m, 1H), 4.63 (s, 1H), 2.25 (s, 3H), 2.13 (s, 3H).

Step E(a)



A 5-L flask is equipped with a heating mantle, air stirrer, condenser, addition funnel, and N_2 inlet/outlet using a Firestone valve. The flask is thoroughly purged with nitrogen, and charged with the compound from Step D (206.0 g, 0.550 moles), DMAC (2.00 L), and molecular sieves (82.4 g) followed by CS_2CO_3 (313.8 g). The reaction is stirred for 15 minutes, and the compound obtained from Step A (137.4 g, 0.660 moles) is added to the mixture. The mixture is heated to about130°C. After about 48 hrs, the reaction is completed, and the mixture is cooled to room temperature. MTBE (3.0 L) is added to the mixture, and then the contents are filtered through Hyflo. After washing the filter cake with MTBE (2 x 0.50 L), the filtrates are transferred to a separatory funnel, and then 1N aq. HCl (2.8 L) is added. The biphasic solution is separated and the top MTBE layer is washed with D.I. H_2O. The bottom 1N HCl solution is back extracted with MTBE (2.0L), and the MTBE is washed with D.I. H_2O (1.0 L). The MTBE layers are combined, dried over Na_2SO_4, and filtered to remove the drying agent. The filtrate is concentrated to give the crude ester compound as an oil (330.0 g, 106.6%).

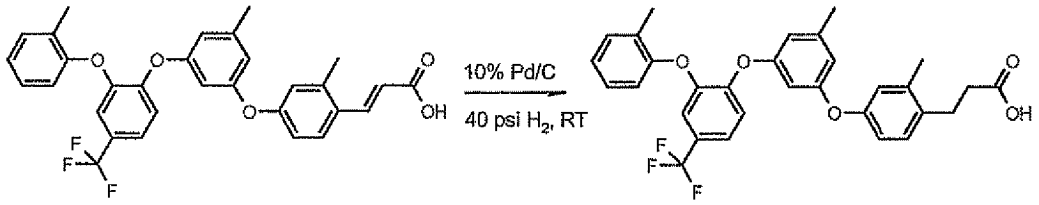
Step E(b)



A 12-L reaction flask is equipped with a heating mantle, air stirrer, condenser, addition funnel, and N_2 inlet/outlet using a Firestone valve. The flask is

thoroughly purged with nitrogen, and then charged the compound obtained from Step E(a) (330.0 g, 0.0.617 moles), EtOH (3.85 L), and 2.5N NaOH (0.88 L). The mixture is heated to about 65°C for 1 hr. The solution is transferred to a Buchi flask and concentrated to a thick slurry. After adding D.I. H_2O (2.75 L) to form a slurry of fine solids, 1N aq. HCl (2.93 L) is added until about pH =1 is obtained. The solution is extracted with MTBE (6.0 L), and the MTBE layer is washed with aq. saturated NaCl (1.4 L) and 1N aq. HCl (0.37 L). After drying the MTBE layer over Na_2SO_4, the drying agent is filtered off, and the filtrate is concentrated to afford crude acid compound (317 g). The crude acid compound is dissolved in acetonitrile (ACN) (15 volumes, 4.75 L) at 65°C, and then slowly cooled to rt overnight. The mixture is filtered, washed with ACN (0.50 L), and dried to yield the final product (214.2 g) as an off-white solid. ^{1}H-NMR($CDCl_3$, 300MHz) δ 12.42 (s, 1H), 7.52 (d, 1H), 7.35 (d, 1H), 7.27 (d, 1H), 7.20-7.10 (m, 2H), 7.10-7.00 (m, 1H), 6.90-6.84 (m, 1H), 6.79 (d, 2H), 6.60 (d, 2H), 6.45-6.28 (m, 3H), 2.32 (s, 3H), 2.22 (s, 3H), 2.04 (s, 3H).

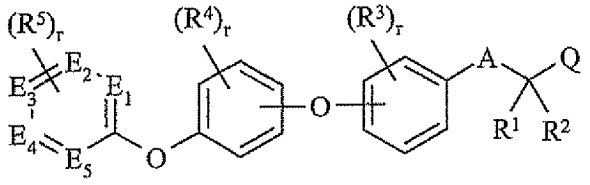
Step F



A 3-gallon autoclave (T85) is charged with 10% Pd/C (15.2 g), ethyl alcohol (4.56 L), and the compound obtained from Step E(b) (304.3 g, 0.569 moles) under H_2 pressure of 40 psi. The mixture is stirred at rt for about 1 hr. The mixture is filtered to remove palladium. The clear filtrate is concentrated to afford the final acid compound (296.3 g, 97.0 %) as a thick oil. ^{1}H-NMR($CDCl_3$, 300MHz) δ 7.36-7.00 (m, 7H), 6.86-6.70 (m, 3H), 6.56-6.36 (m, 3H), 2.92 (t, 2H), 2.62 (t, 2H), 2.28 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H).

WHAT IS CLAIMED IS:

1. A compound having a formula I,



I

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

E_1, E_2, E_3, E_4 and E_5 are each CH or substituted carbon bearing R^5; or at least one of E_1, E_2, E_3, E_4 and E_5 is nitrogen and each of others being CH or substituted carbon bearing R^5;

A is: a bond, CH_2, $(CH_2)_2$, O, S; or A and R^1 or A and R^2 together being a 3- to 6-membered carbocyclyl when A is a carbon;

Q is: $-C(O)OR^6$ or R^{6A};

n is: 1, 2, 3, 4, 5 or 6

p is: 1 or 2;

r is: 1, 2, 3, or 4;

R^1 and R^2 are each independently:

hydrogen, C_1-C_6 alkyl, or R^1 and R^2 together being a 3- to 8-membered carbocyclic ring;

R^3 and R^4 are each independently:

hydrogen,

nitro,

cyano,

hydroxyl,

halo,

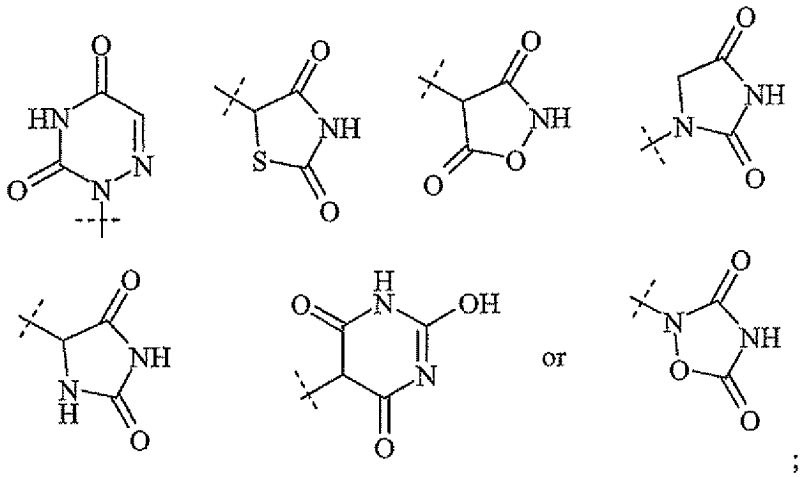
haloalkyl,
haloalkyloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy, or
C_3-C_8 cycloalkyl

R^5 is: hydrogen,
nitro,
cyano,
hydroxyl,
halo,
haloalkyl,
haloalkyloxy,
aryloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy,
[T]-aryl,
[T]-heteroaryl,
[T]-heterocyclyl,
[T]-$(CH_2)_nC_3$-C_8 cycloalkyl,
$C(O)_pR^7$,
$O(CH_2)_nR^7$,
SR^7,
$S(O)_pR^7$ or
$OS(O)_pR^7$,
wherein aryl, aryloxy, alkyl, heteroaryl, heterocyclyl and cycloalkyl are being optionally substituted with one or more substituents independently selected from R^8;

[T] is: a bond, O, C(O), S, NR^7, or C_1-C_6 alkyl;

R^6 is: hydrogen, C_1-C_6 alkyl or aminoalkyl;

R^{6A} is: carboxamide, sulfonamide, acylsulfonamide, tetrazole,



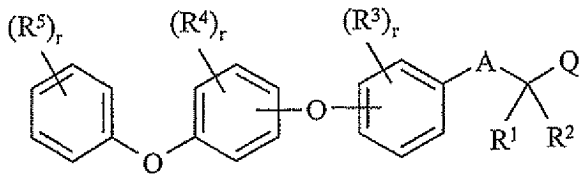
or

;

R^7 is: hydrogen,
C_1-C_6 alkyl,
C_3-C_8 cycloalkyl,
aryl,
heteroaryl or
heterocyclyl,
wherein alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl being optionally substituted with one or more substituents independently selected from R^8; and

R^8 is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, acyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or C_3-C_8 cycloalkyl.

2. The compound of Claim 1, wherein the compound having a formula II,



II

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

A is: a bond, CH_2, $(CH_2)_2$, O, S; or A and R^1 or A and R^2 together being a 3- to 6-membered carbocyclyl when A is a carbon;

Q is: $-C(O)OR^6$ or R^{6A};

n is: 1, 2, 3, 4, 5 or 6

p is: 1 or 2;

r is: 1, 2, 3, or 4;

R^1 and R^2 are each independently:

hydrogen, C_1-C_6 alkyl, or R^1 and R^2 together being a 3- to 8-membered carbocyclic ring;

R^3 and R^4 are each independently:

hydrogen,
nitro,
cyano,
hydroxyl,
halo,
haloalkyl,
haloalkyloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy, or
C_3-C_8 cycloalkyl;

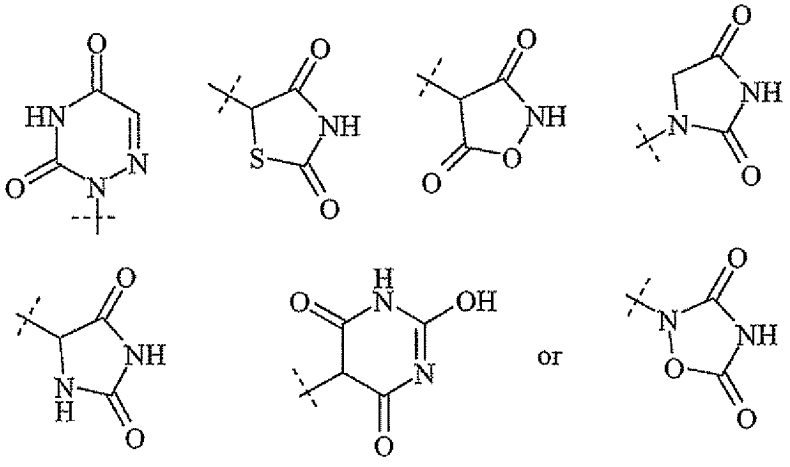
R^5 is: hydrogen,
nitro,
cyano,
hydroxyl,
halo,
haloalkyl,

haloalkyloxy,
aryloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy,
[T]-aryl,
[T]-heteroaryl,
[T]-heterocyclyl,
[T]-$(CH_2)_nC_3$-C_8 cycloalkyl,
$C(O)_pR^7$,
$O(CH_2)_nR^7$,
SR^7,
$S(O)_pR^7$ or
$OS(O)_pR^7$,
wherein aryl, aryloxy, alkyl, heteroaryl, heterocyclyl and cycloalkyl are being optionally substituted with one or more substituents independently selected from R^8;

[T] is: a bond, O, C(O), S, NR^7, or C_1-C_6 alkyl;

R^6 is: hydrogen, C_1-C_6 alkyl or aminoalkyl;

R^{6A} is: carboxamide, sulfonamide, acylsulfonamide, tetrazole,



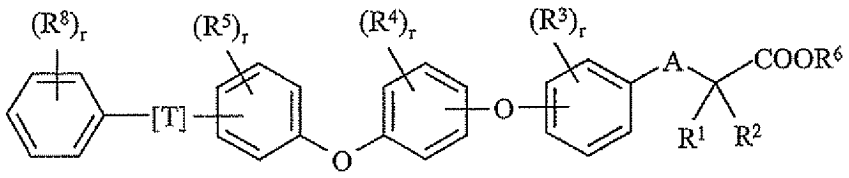
or

;

R^7 is: hydrogen,
C_1-C_6 alkyl,
C_3-C_8 cycloalkyl,
aryl,
heteroaryl or
heterocyclyl,
wherein alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl being optionally substituted with one or more substituents independently selected from R^8; and

R^8 is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, acyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or C_3-C_8 cycloalkyl.

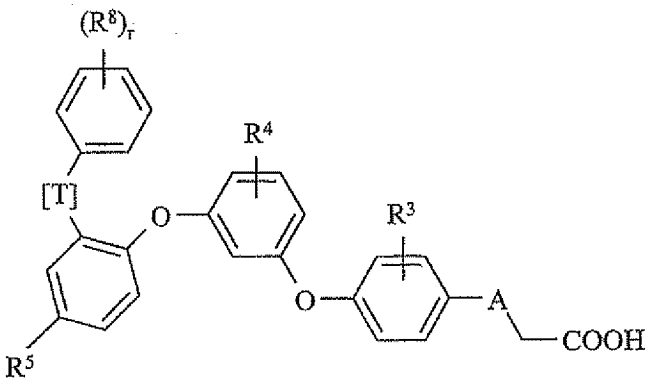
3. The compound of Claim 2, wherein the compound having a structural formula III,



III

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

4. The compound of Claim 3, wherein the compound having a structural formula IV,



IV

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

A is: CH_2, O, S;

[T] is: a bond, O, C(O) or C_1-C_3 alkyl;

R^3 and R^4 are each independently:

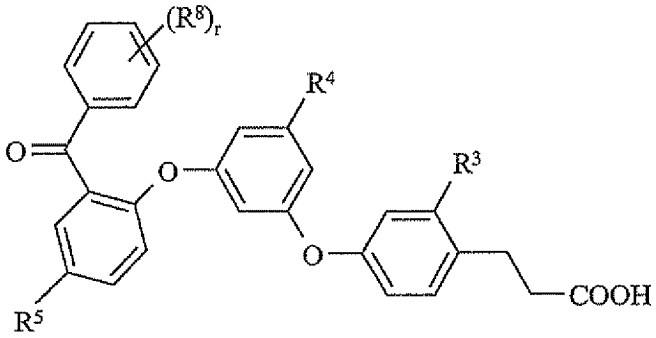
hydrogen, C_1-C_3 alkyl, halo, haloalkyl or haloalkyloxy;

R^5 and R^8 are each independently:

hydrogen, C_1-C_6 alkyl, halo, haloalkyl or haloalkyloxy; and

r is 1 or 2.

5. The compound of Claim 4, wherein the compound having a structural formula V,



V

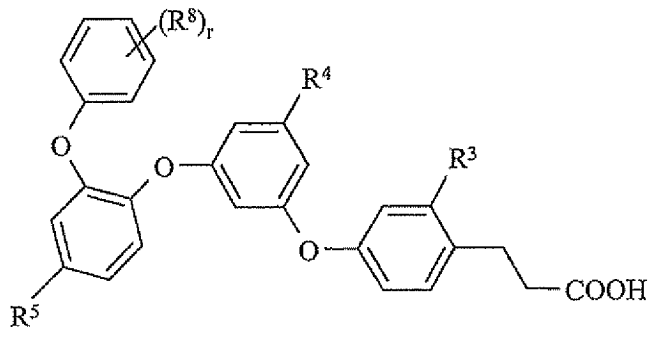
or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;

R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and

r is 1 or 2.

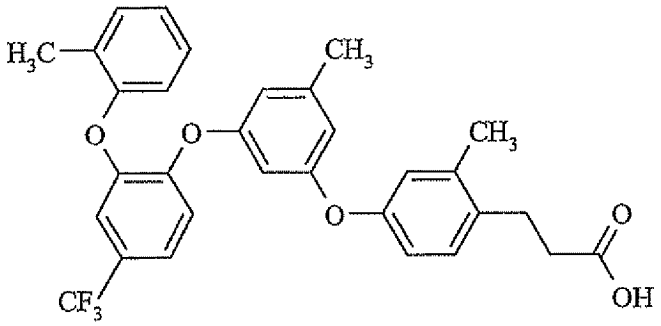
6. The compound of Claim 4, wherein the compound having a structural formula VI,



VI

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:
R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;
R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and
r is 1 or 2.

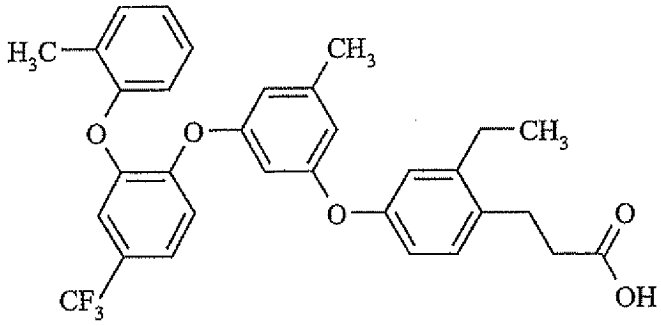
7. The compound of Claim 6, wherein the compound having a wherein the compound having a structural formula VII,



VII

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

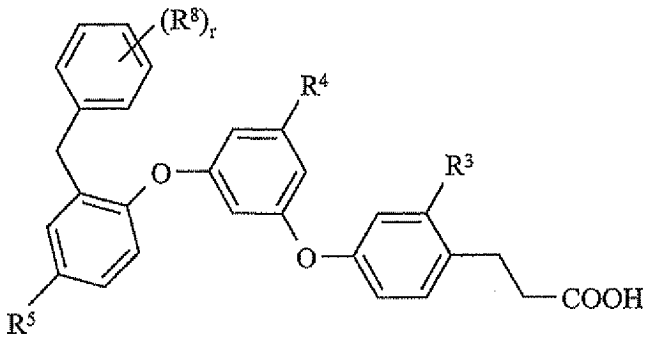
8. The compound of Claim 6, wherein the compound having a wherein the compound having a structural formula VIII,



VIII

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

9. The compound of Claim 4, wherein the compound having a structural formula IX,



IX

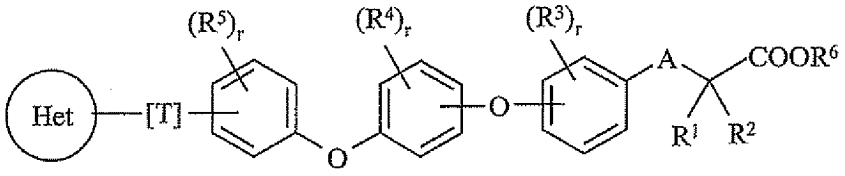
or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;

R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and

r is 1 or 2.

10. The compound of Claim 2, wherein the compound having a structural formula X,



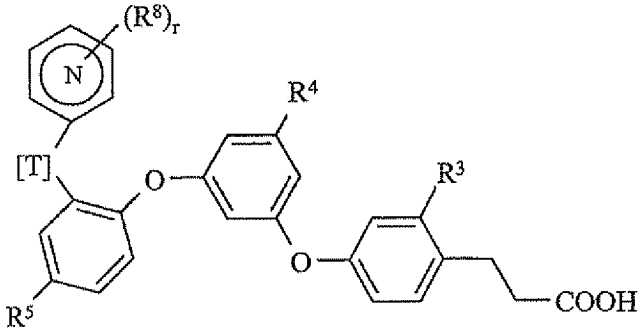
X

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

is a 5- or 6-membered heteroaryl or heterocyclyl, wherein heteroaryl and heterocyclyl being optionally substituted with one or more substituents independently selected from R^8.

11. The compound of Claim 10, wherein the heteroaryl is pyrazolyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl or pyrimidinyl

12. The compound of Claim 10, wherein the compound having a structural formula XI,



XI

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

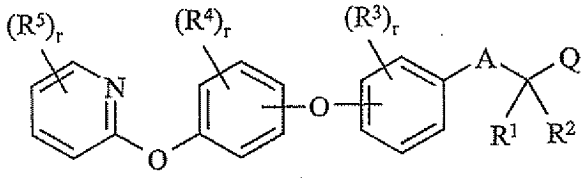
[T] is: a bond, O, C(O) or C_1-C_3 alkyl;

R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;

R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and

r is 1 or 2.

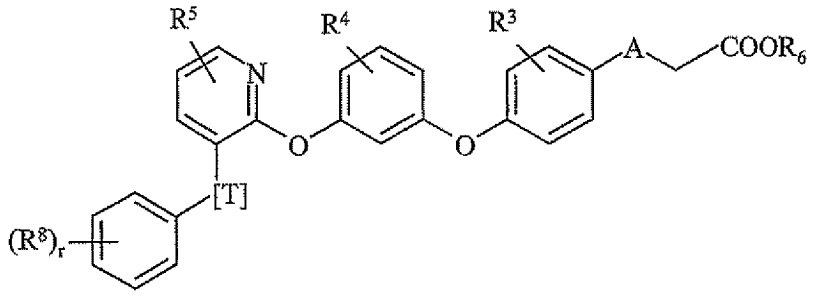
13. The compound of Claim 1, wherein the compound having a formula XII,



XII

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

14. The compound of Claim 13, wherein the compound having a formula XIII,



XIII

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

A is: CH_2, O, S;

[T] is: a bond, O, C(O) or C_1-C_3 alkyl;

R^3 and R^4 are each independently:

hydrogen, C_1-C_3 alkyl, halo, haloalkyl or haloalkyloxy;

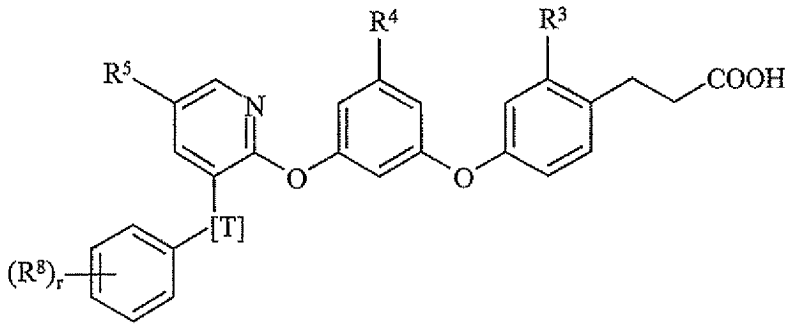
R^5 and R^8 are each independently:

hydrogen, C_1-C_6 alkyl, halo, haloalkyl or haloalkyloxy; and

R^6 is: hydrogen or C_1-C_6 alkyl; and

r is 1 or 2.

15. The compound of Claim 14, wherein the compound having a formula XIV,



XIV

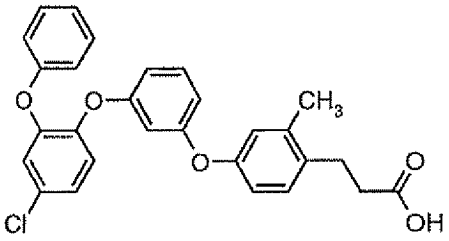
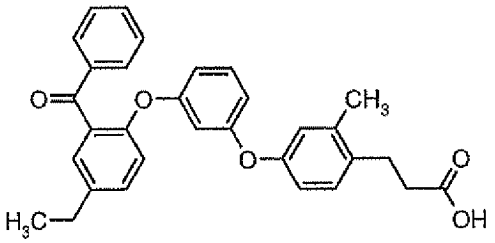
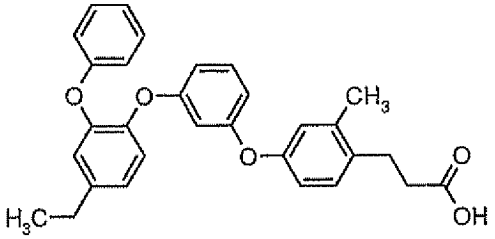
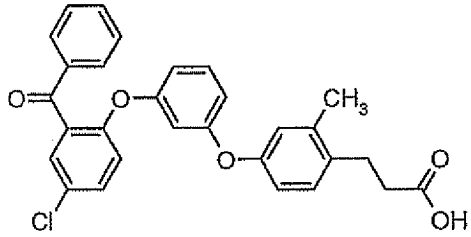
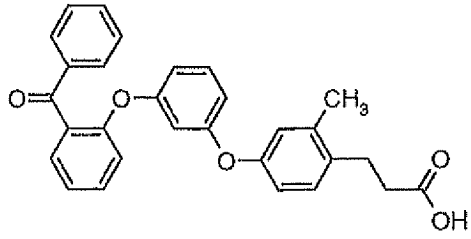
or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

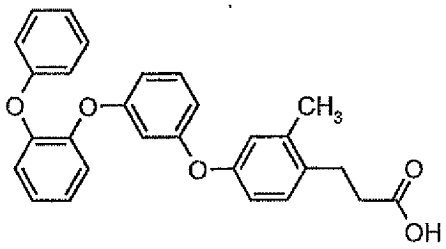
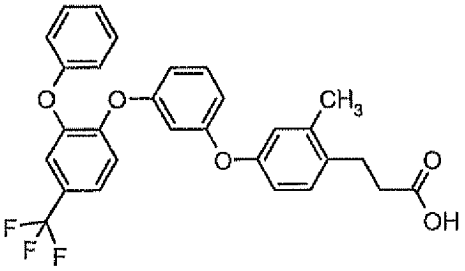
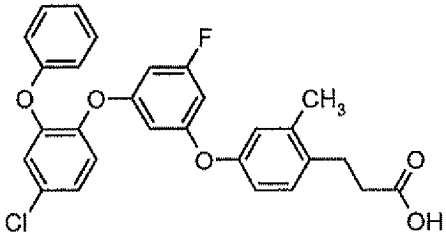
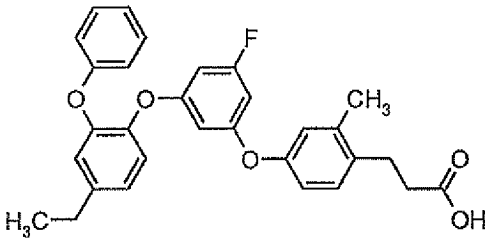
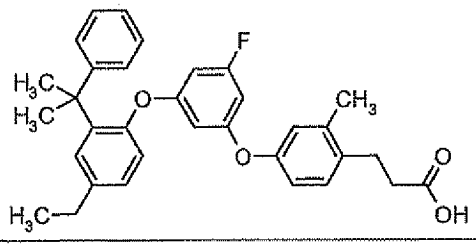
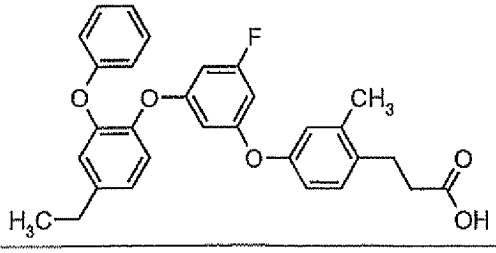
[T] is: a bond, O or C_1-C_3 alkyl;

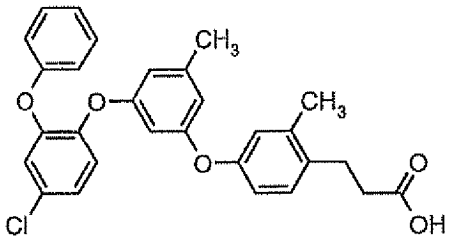
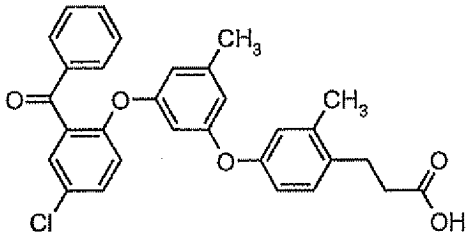
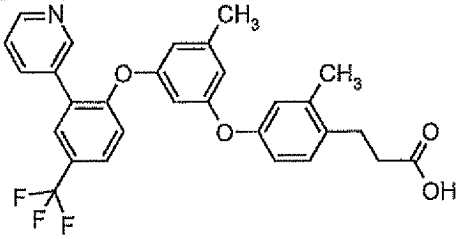
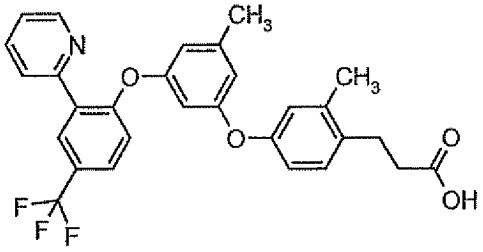
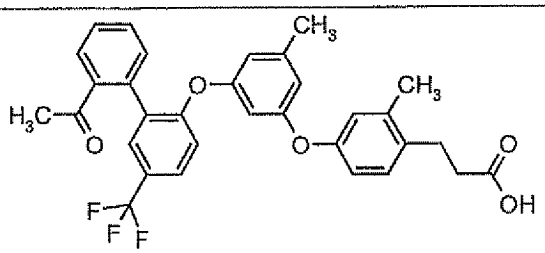
R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;

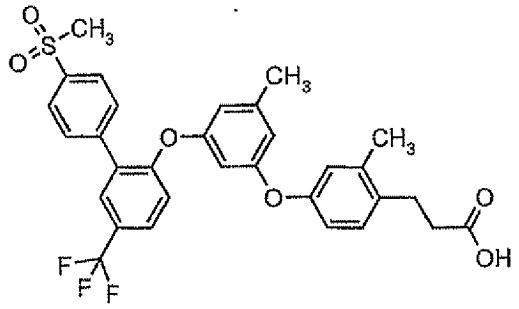
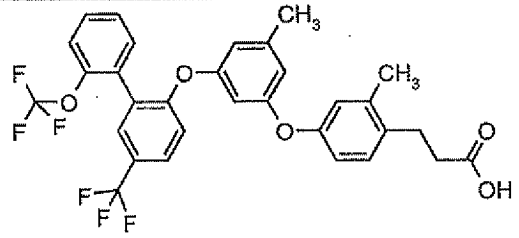
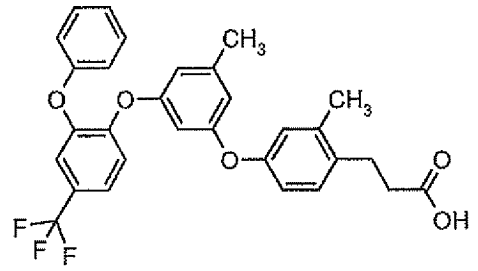
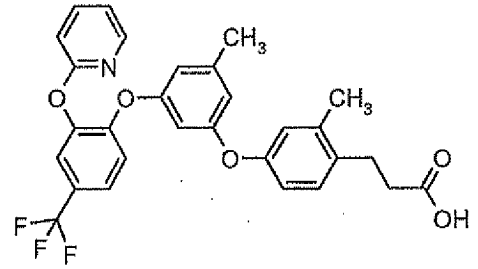
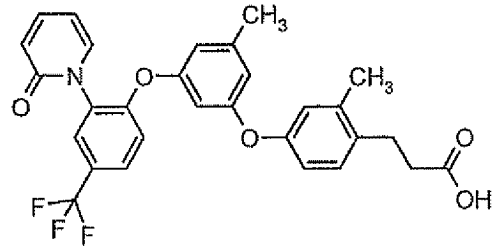
R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and r is 1 or 2.

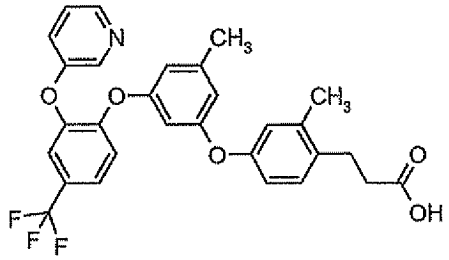
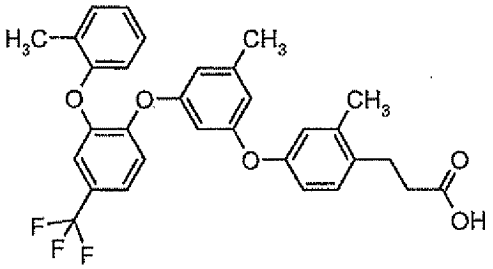
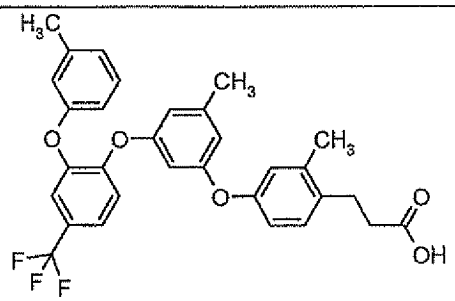
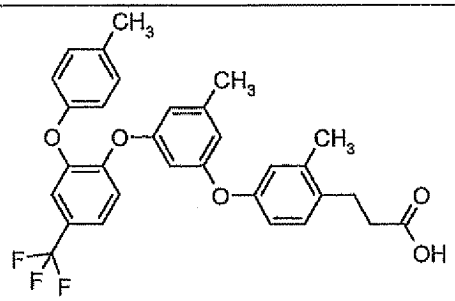
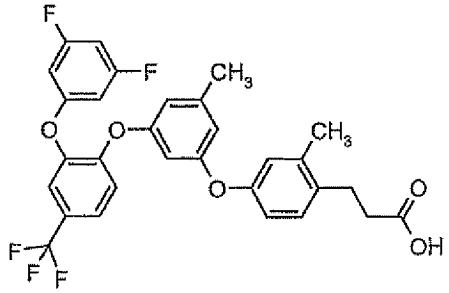
16. A compound selected from the group consisting of the following compounds:

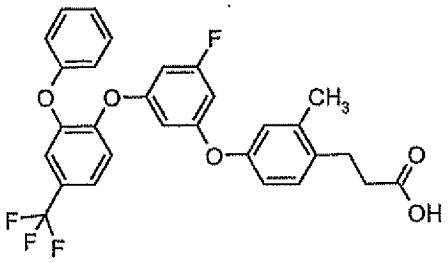
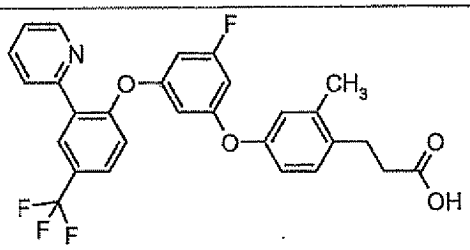
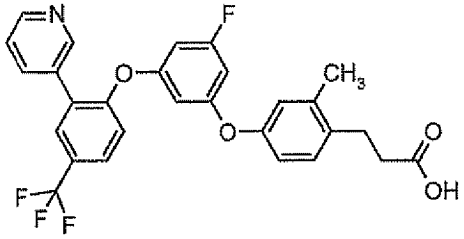
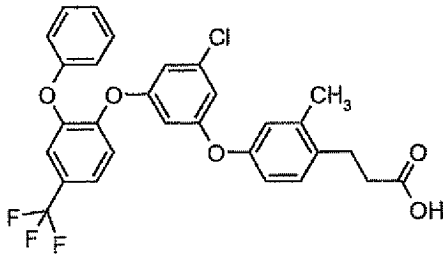
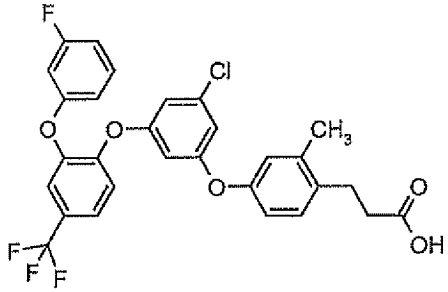
No.	Structure	Name
1		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
2		3-{4-[3-(2-Benzoyl-4-ethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
3		3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
4		3-{4-[3-(2-Benzoyl-4-chloro-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
5		3-{4-[3-(2-Benzoyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid

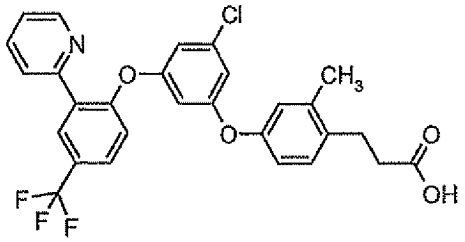
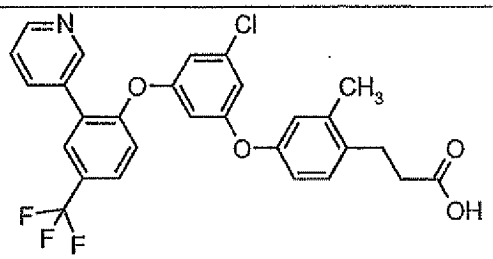
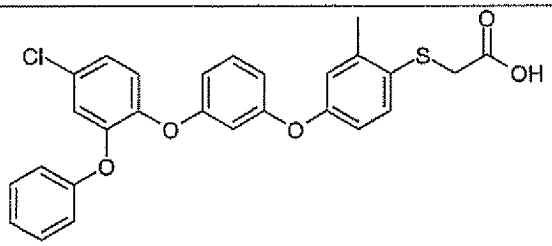
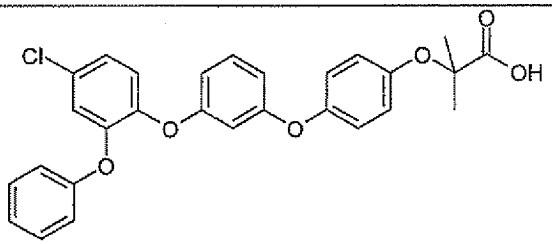
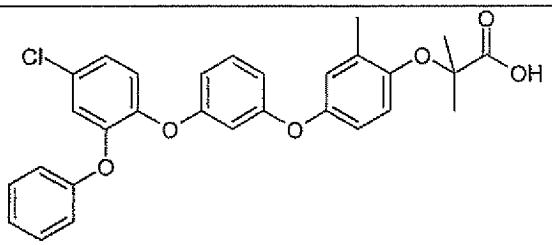
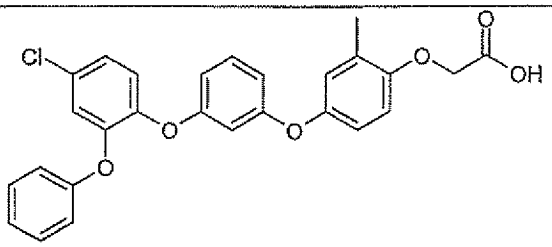
No.	Structure	Name
6		3-{2-Methyl-4-[3-(2-phenoxy-phenoxy)-phenoxy]-phenyl}-propionic acid
7		3-{2-Methyl-4-[3-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
8		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid
9		3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid
10		3-(4-{3-[4-Ethyl-2-(1-methyl-1-phenyl-ethyl)-phenoxy]-5-fluoro-phenoxy}-2-methyl-phenyl)-propionic acid
11		3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid

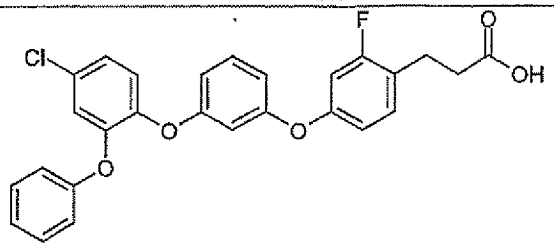
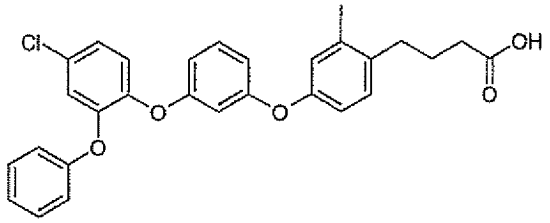
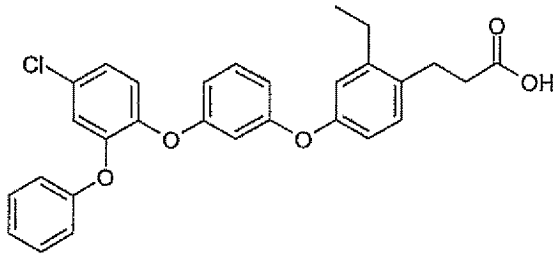
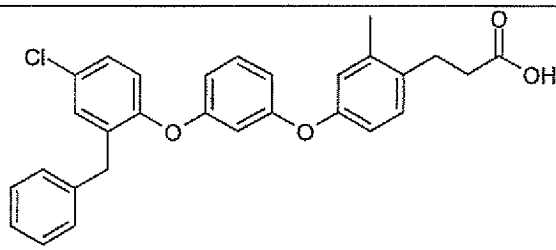
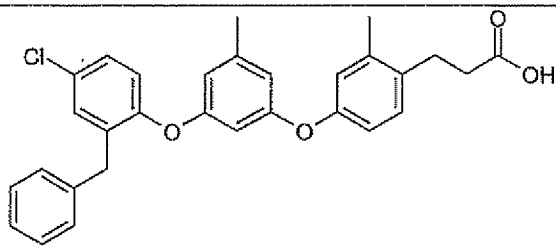
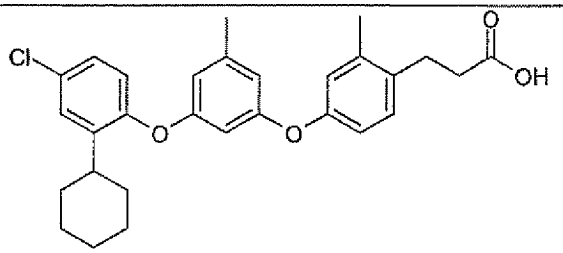
No.	Structure	Name
12		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
13		3-{4-[3-(2-Benzoyl-4-chloro-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
14		3-{2-Methyl-4-[3-methyl-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
15		3-{2-Methyl-4-[3-methyl-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
16		3-{4-[3-(2'-Acetyl-5-trifluoromethyl-biphenyl-2-yloxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid

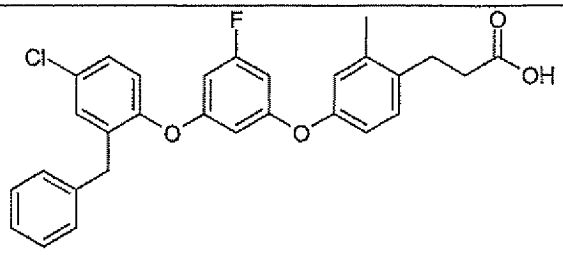
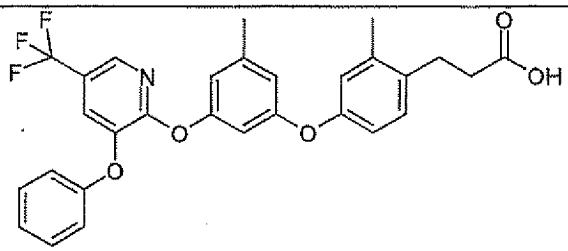
No.	Structure	Name
17		3-{4-[3-(4'-Methanesulfonyl-5-trifluoromethyl-biphenyl-2-yloxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
18		3-{2-Methyl-4-[3-methyl-5-(2'-trifluoromethoxy-5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-phenyl}-propionic acid
19		3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
20		3-(2-Methyl-4-{3-methyl-5-[2-(pyridin-2-yloxy)-4-trifluoromethyl-phenoxy]-phenoxy}-phenyl)-propionic acid
21		3-(2-Methyl-4-{3-methyl-5-[2-(2-oxo-2H-pyridin-1-yl)-4-trifluoromethyl-phenoxy]-phenoxy}-phenyl)-propionic acid

No.	Structure	Name
22		3-(2-Methyl-4-{3-methyl-5-[2-(pyridin-3-yloxy)-4-trifluoromethyl-phenoxy]-phenoxy}-phenyl)-propionic acid
23		3-{2-Methyl-4-[3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
24		3-{2-Methyl-4-[3-methyl-5-(2-m-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
25		3-{2-Methyl-4-[3-methyl-5-(2-p-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
26		3-(4-{3-[2-(3,5-Difluoro-phenoxy)-4-trifluoromethyl-phenoxy]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid

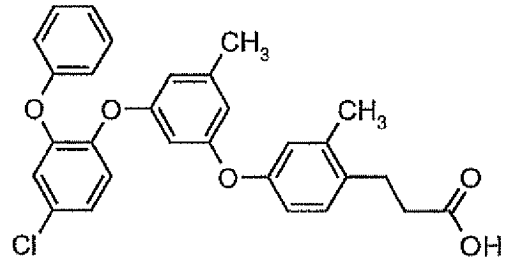
No.	Structure	Name
27		3-{4-[3-Fluoro-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
28		3-{4-[3-Fluoro-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
29		3-{4-[3-Fluoro-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
30		3-{4-[3-Chloro-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
31		3-(4-{3-Chloro-5-[2-(3-fluoro-phenoxy)-4-trifluoromethyl-phenoxy]-phenoxy}-2-methyl-phenyl)-propionic acid

No.	Structure	Name
32		3-{4-[3-Chloro-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
33		3-{4-[3-Chloro-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
34		{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenylsulfanyl}-acetic acid
35		2-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-phenoxy}-2-methyl-propionic acid
36		2-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid
37		{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenoxy}-acetic acid

No.	Structure	Name
38		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-fluoro-phenyl} -propionic acid
39		4-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl} -butyric acid
40		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-ethyl-phenyl}-propionic acid
41		3-{4-[3-(2-Benzyl-4-chloro-phenoxy)-phenoxy]-2-methyl-phenyl} -propionic acid
42		3-{4-[3-(2-Benzyl-4-chloro-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
43		3-{4-[3-(4-Chloro-2-cyclohexyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid

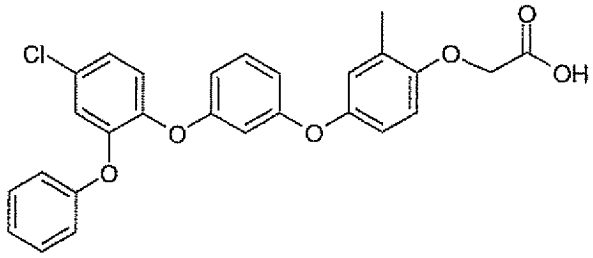
No.	Structure	Name
44		3-{4-[3-(2-Benzyl-4-chloro-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid
45		3-{2-Methyl-4-[3-methyl-5-(3-phenoxy-5-trifluoromethyl-pyridin-2-yloxy)-phenoxy]-phenyl}-propionic acid

17. The compound of Claim 16, wherein the compound is 3-{4-[3-(4-chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid



or a pharmaceutically acceptable salt, solvate or hydrate thereof.

18. The compound of Claim 16, wherein the compound is: {4-[3-(4-chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenoxy}-acetic acid



or a pharmaceutically acceptable salt, solvate or hydrate thereof.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Claims 1-18 or a pharmaceutically acceptable salt, solvate or hydrate thereof.

20. A pharmaceutical composition comprising:

(1) a compound of Claims 1-18, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof;

(2) a second therapeutic agent selected from the group consisting of: insulin sensitizers, sulfonylureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin; and

(3) optionally a pharmaceutically acceptable carrier.

21. A method of modulating a peroxisome proliferator activated receptor (PPAR), comprising the step of contacting the receptor with a compound of Claims 1-18, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

22. The method of Claim 21, wherein the PPAR is an alpha (α)-receptor.

23. The method of Claim 21, wherein the PPAR is a gamma (γ)-receptor.

24. The method of Claim 21, wherein the PPAR is a delta (δ)-receptor.

25. The method of Claim 21, wherein the PPAR is a gamma/delta (γ/δ)-receptor.

26. The method of Claim 21, wherein the PPAR is a alpha/gamma/delta (α/γ/δ)-receptor.

27. A method for treating a PPARγ-mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of Claims 1-18.

28. A method for treating a PPARδ-mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of Claims 1-18.

29. A method for treating a PPARγ/δ-mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of Claims 1-18.

30. A method for treating a PPARα/γ/δ-mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of Claims 1-18.

31. A method for lowering blood-glucose in a mammal comprising the step of administering an effective amount of a compound of Claims 1-18.

32. A method of treating disease or condition in a mammal selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of a compound of Claims 1-18.

33. A method of treating diabetes mellitus in a mammal comprising the step of administering to a mammal a therapeutically effective amount of a compound of Claims 1-18.

34. A method of treating cardiovascular disease in a mammal comprising the step of administering to a mammal a therapeutically effective amount of a compound of Claims 1-18, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

35. A method of treating syndrome X in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of a compound of Claims 1-18, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

36. A method of treating disease or condition in a mammal selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of a compound of Claims 1-18 and an effective amount of second therapeutic agent selected from the group consisting of: insulin sensitizers, sulfonylureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

37. Use of a compound of Claims 1-18, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof for the manufacture of a medicament for the treatment of a condition modulated by a PPAR.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/030911

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C53/134 C07C59/135 C07D213/69 C07D213/30 C07D213/64
C07D239/26 A61K31/435 A61K31/19 A61K31/21 A61P3/10
C07D213/643

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, PAJ, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/093799 A (BRISTOL-MYERS SQUIBB COMPANY; RYONO, DENNIS, E; HANGELAND, JON, J; FRI) 4 November 2004 (2004-11-04) abstract page 57 - page 62; examples 65-98 claims	1-37
P,X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HUTTER, MICHAEL C. ET AL: "QSAR of human steroid 5.alpha.-reductase inhibitors: Where are the differences between isoenzyme type 1 and 2?" XP002318310 retrieved from STN Database accession no. 2004:665197 abstract -/--	1,19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2005	03/03/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stix-Malaun, E

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	JP 08 059638 A (YAMANOUCHI PHARMA CO LTD, JAPAN) 5 March 1996 (1996-03-05) abstract page 23; example 4 page 25; example 13 claims	1-37
X	EP 0 696 585 A (YAMANOUCHI PHARMACEUTICAL CO. LTD) 14 February 1996 (1996-02-14) abstract page 73; example 9 page 75; examples 31-37 page 76; examples 40-46 page 77; examples 48-50,52-55 claims	1-37
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X	EP 0 307 103 A (IMPERIAL CHEMICAL INDUSTRIES PLC; ZENECA LIMITED) 15 March 1989 (1989-03-15) page 71, line 8 - line 9 page 73; figure III page 92, line 17; example 7	1

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/030911

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CREWS, A. D. ET AL: "Synthesis and herbicidal activity of bisaryloxybenzenes: a new structural class of protox inhibitors derived from N-phenylbenzotriazoles" ACS SYMPOSIUM SERIES , 686(SYNTHESIS AND CHEMISTRY OF AGROCHEMICALS V), 48-54 CODEN: ACSMC8; ISSN: 0097-6156, 1998, XP009044229 page 49; figure 1 Scheme I page 50 page 53; table I	1
A	EBISAWA M ET AL: "THIAZOLIDINEDIONES WITH THYROID HORMONE RECEPTOR AGONISTIC ACTIVITY" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 47, no. 9, 1999, pages 1348-1350, XP000906992 ISSN: 0009-2363 the whole document	1-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/030911

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ormation on patent family members

International Application No
PCT/US2004/030911

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AT 175409 T	15-01-1999
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Interna[illegible]nal Application No
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		DE 3887603 D1	17-03-1994
		DE 3887603 T2	26-05-1994
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